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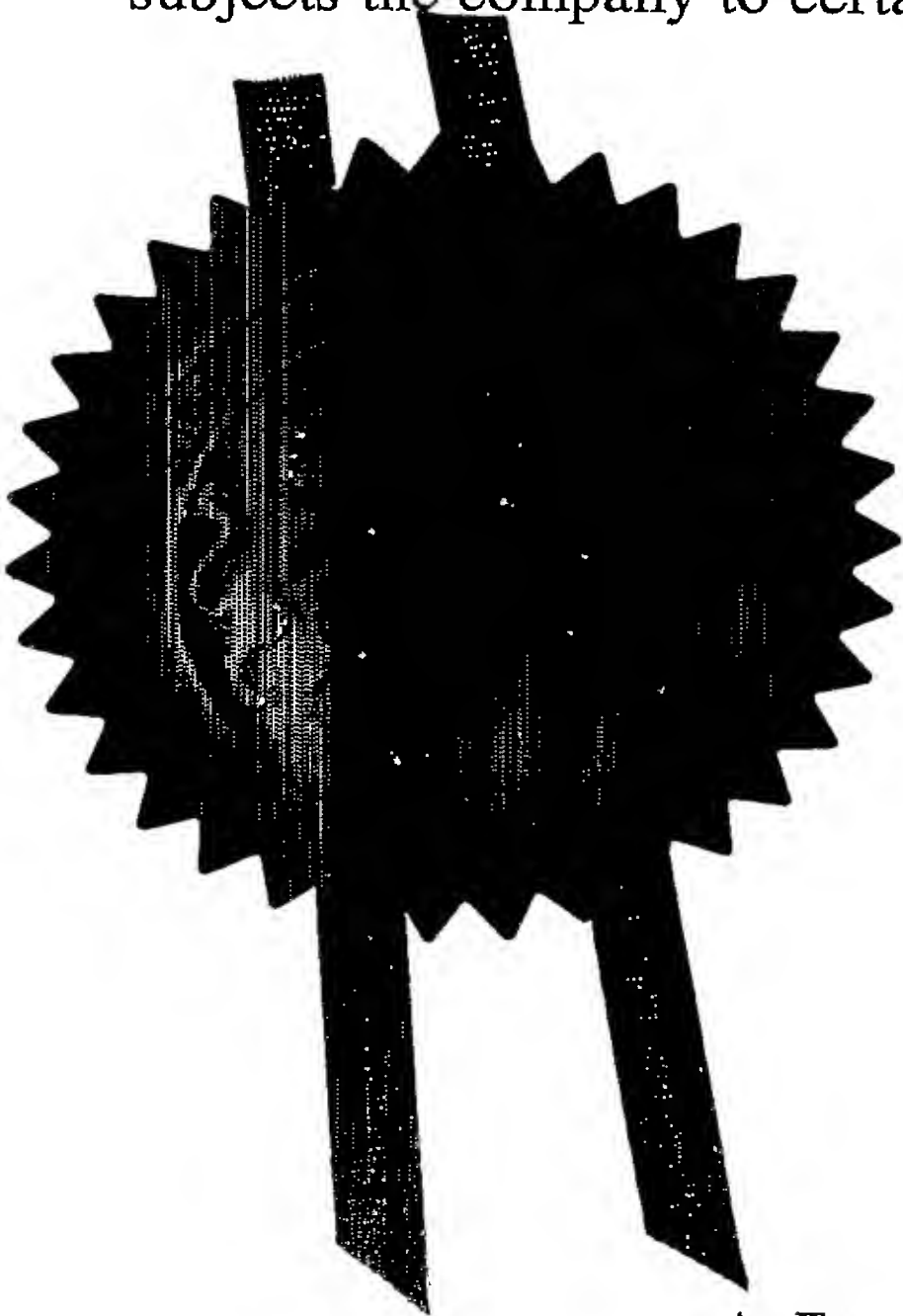
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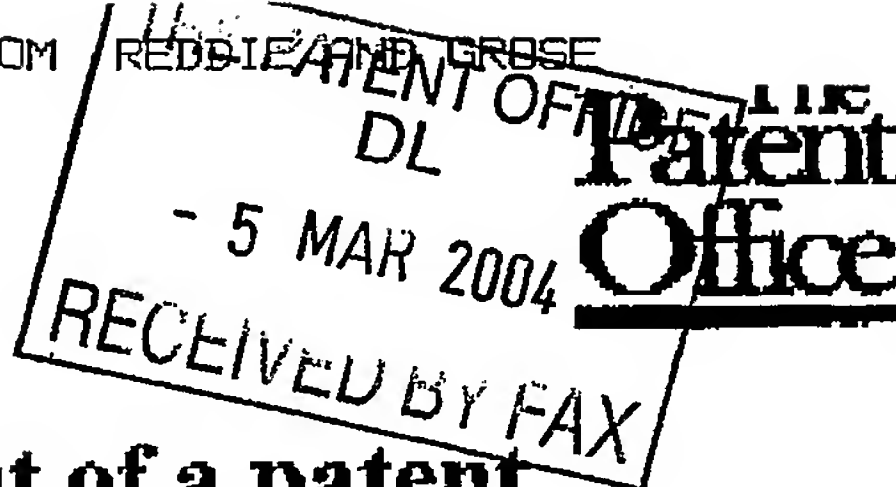


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47628.GB01/NT

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0405012.6

3. Full name, address and postcode of the or of
each applicant (underline all surnames)Cambridge Biotechnology Ltd
P.O. Box 230
Cambridge
CB2 1XJ
United Kingdom

Patents ADP number (if you know it)

If the applicant is a corporate body, give the
country/state of incorporation

United Kingdom

8208761002

4. Title of the invention

Therapeutic Compounds

5. Full name, address and postcode in the United
Kingdom to which all correspondence relating
to this form and translation should be sentReddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number (if you know it)

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Priority application
(if you know it)Date of filing
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Reddie & Grose

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47268.GB01

Therapeutic Compounds

This invention relates to use of adenosine receptor agonists as therapeutic compounds.

Adenosine is a ubiquitous local hormone/neurotransmitter that acts on four known receptors, the adenosine A1, A2A, A2B and A3 receptors. Adenosine generally serves to balance the supply and demand of energy in tissues. For example, in the heart released adenosine slows the heart by an A1 receptor mediated action in the nodes and atria (Belardinelli, L & Isenberg, G Am. J. Physiol. 224, H734-H737), while simultaneously dilating the coronary artery to increase energy (i.e. glucose, fat and oxygen) supply (Knabb et al., Circ. Res. (1983) 53, 33-41). Similarly, during inflammation adenosine serves to inhibit inflammatory activity, while in conditions of excessive nerve activity (e.g. epilepsy) adenosine inhibits nerve firing (Klitgaard et al., Eur J. Pharmacol. (1993) 242, 221-228). This system, or a variant on it, is present in all tissues.

Adenosine itself can be used to diagnose and treat supraventricular tachycardia. Adenosine A1 receptor agonists are known to act as powerful analgesics (Sawynok, J. Eur J Pharmacol. (1998) 347, 1-11). Adenosine A2A receptor agonists are known to act as anti-inflammatory agents (for example, from US 5,877,180 and WO 99/34804). In experimental animals, A2A receptor agonists have been shown to be effective against a wide variety of conditions including sepsis, arthritis, and ischaemia/reperfusion injury arising from renal, coronary or cerebral artery occlusion. The common factor in these conditions is a reduction in the inflammatory response caused by the inhibitory effect of this receptor on most, if not all, inflammatory cells.

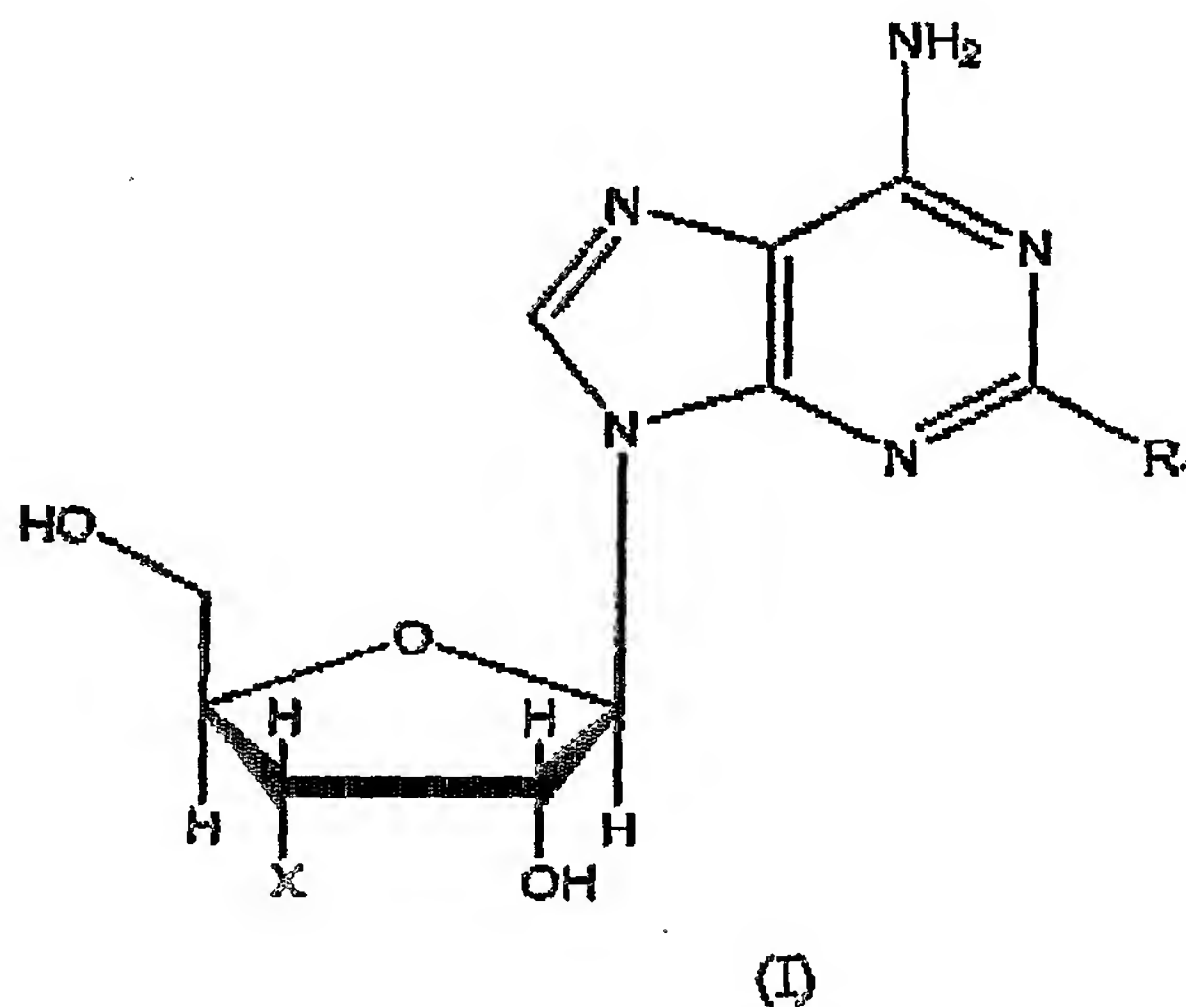
However, the ubiquitous distribution of adenosine receptors means that administration of adenosine receptor agonists causes adverse side effects. This has generally precluded the development of adenosine-based therapies. Selective A1 receptor agonists cause bradycardia. The first selective A2A receptor agonist (2-[4-(2-carboxyethyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine, or CGS21680), was tested in a Phase 2A clinical trial as a potential anti-hypertensive. However,

administration caused a large fall in blood pressure and consequent increase in cardiac output. FR 2162128 discloses that adenosine derivatives (including 2-alkoxy adenosine derivatives comprising a lower alkyl group of not less than two carbon atoms) have hypotensive and coronary vasodilatory activity.

Bartlett *et al* (J. Med. Chem. 1981, 24, 947-954) discloses the evaluation of analogues of 1-methylisoguanosine. These analogues include 2-methoxyadenosine (also known as spongosine). This and other compounds were tested for their skeletal muscle-relaxant, hypothermic, cardiovascular and anti-inflammatory effects in rodents following oral administration (anti-inflammatory activity was assessed by inhibition of carageenan-induced oedema in a rat paw). 2-methoxyadenosine caused 25% inhibition of carageenan-induced inflammation in rats at 20 mg/kg po. However, reductions in mean blood pressure (41%), and in heart rate (25%) were also observed after administration of this compound at this dose.

There is, therefore, a need to provide adenosine receptor agonists that can be administered with minimal side effects.

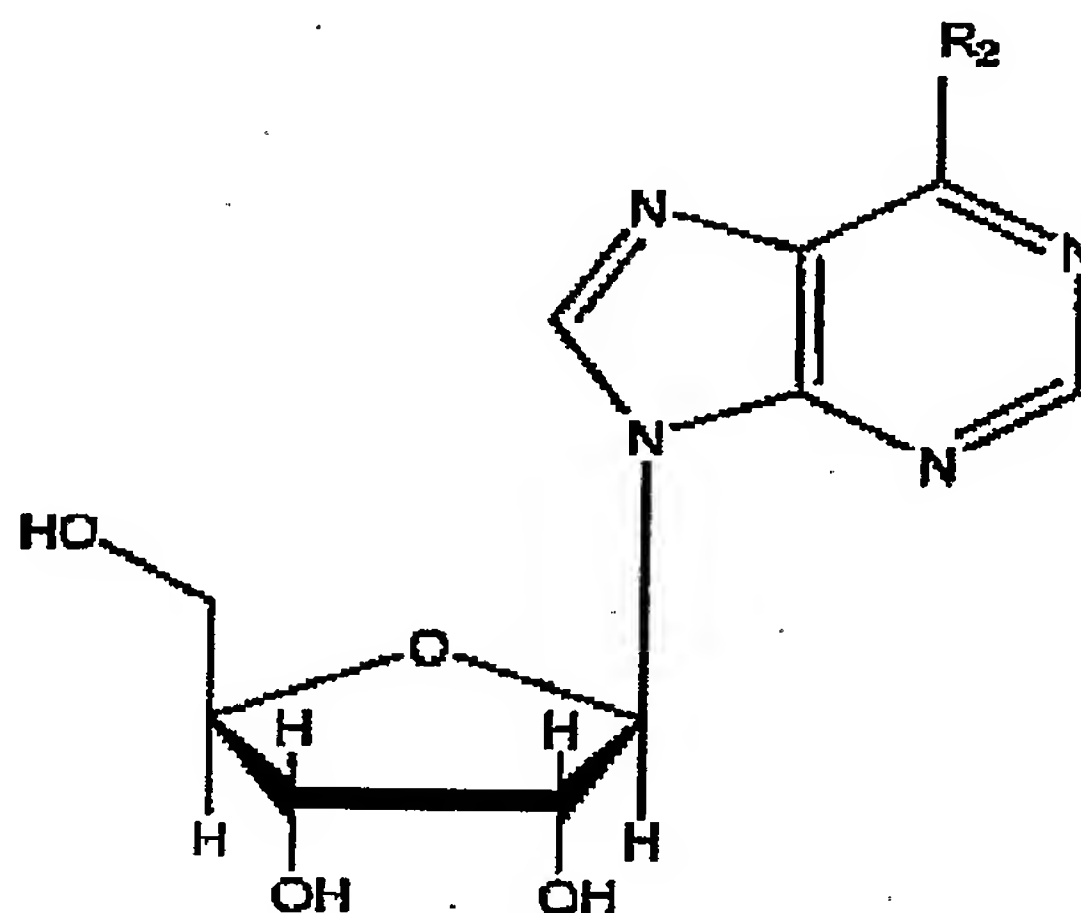
According to the invention there is provided adenosine receptor agonists of the following formulae:



wherein:

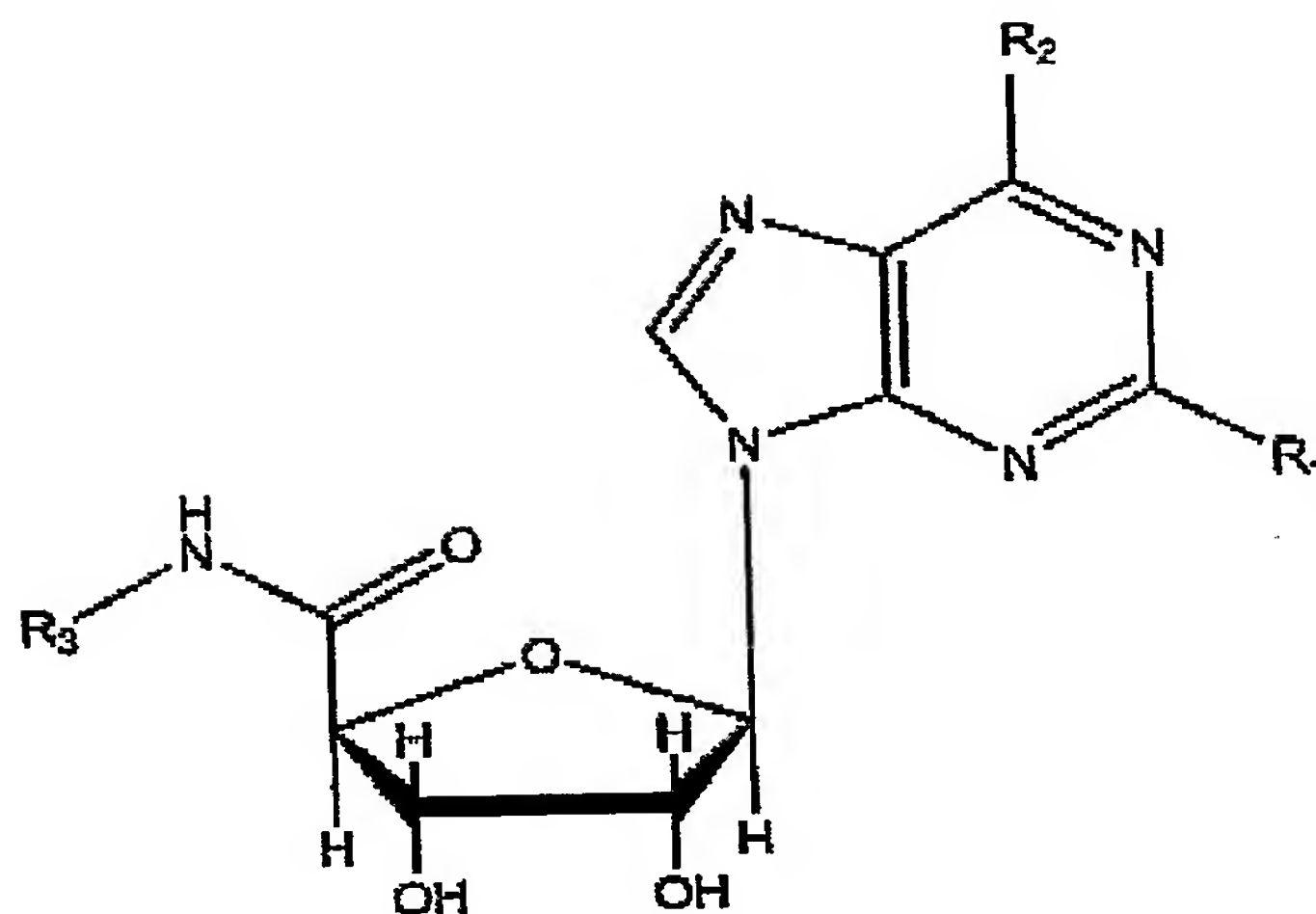
when $X = OH$, R_1 is C_1 or C_4-C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1 , C_2 , C_5 , or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH ; or

when $X = H$, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2 , N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



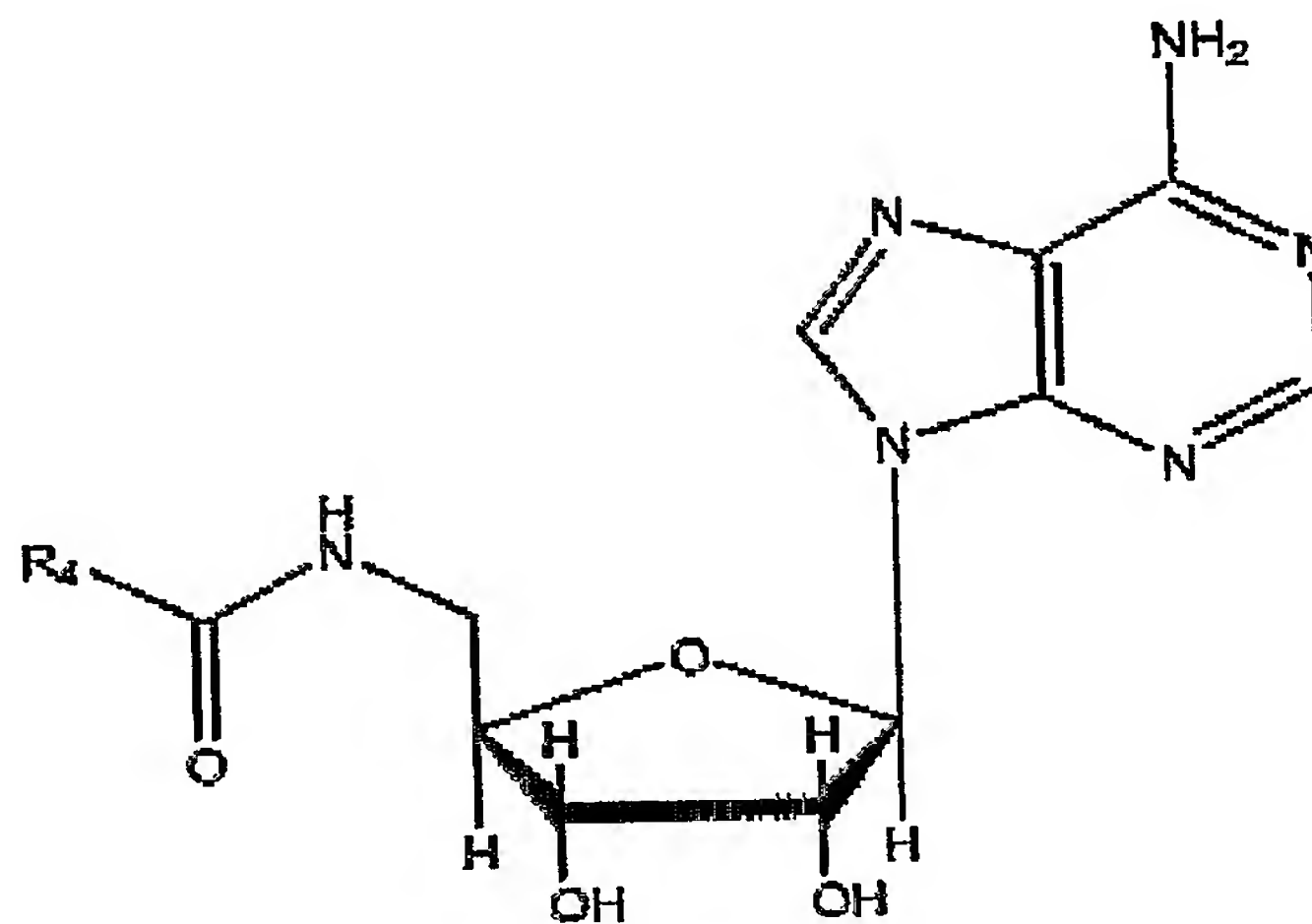
(III)

wherein:

when $R_1 = H$, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group ($NHMe$); or

when $R_1 = H$, R_3 is H , and R_2 is NH_2 ; or

when R_1 is OMe , R_3 is Ph , and R_2 is NH_2 ;



(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$.

There is also provided according to the invention a compound of the invention for use as a medicament.

There is further provided according to the invention use of a compound of the invention for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

There is further provided according to the invention a method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound of the invention to a subject in need of such prevention, treatment, or amelioration.

In particular, it is believed that compounds of the invention can be used to prevent, treat, or ameliorate inflammation caused by or associated with cancer, autoimmune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), psoriasis, asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, organ transplant rejection, cachexia secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria, bacterial meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, and adverse effects from GM-CSF treatment.

Compounds of the invention that are selective agonists of adenosine A2A and/or A3 receptors are particularly preferred because it is believed that such compounds will have strong anti-inflammatory activity. By selective agonists of adenosine A2A and/or A3 receptors is meant agonists that activate adenosine A2A and/or A3 receptors at concentrations that are lower (preferably one thousandth to one fifth) than required to activate adenosine A1 receptors. Furthermore, A1 receptors have pro-inflammatory activity, so such effects are expected to be minimised for compounds that are selective for A2A and/or A3 receptors.

Compounds of the invention are believed to be much more effective at low doses than other adenosine receptor agonists. Thus, it is expected that compounds of the invention can be effectively administered at doses at which they have reduced probability and severity of side effects, or at which side effects are not observed. Such compounds provide significant advantages over the vast majority of other adenosine receptor agonists which only have anti-inflammatory effects at the same concentrations at which serious side effects are observed.

Compounds of the invention may alternatively or additionally have reduced probability and severity of side effects compared to other adenosine receptor agonists.

The amount of a compound of the invention that is administered to a subject should be an amount which gives rise to a peak plasma concentration that is less than the lowest EC50 value of the compound at adenosine receptors (i.e. less than the lowest EC50 value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value.

Preferably the amount of a compound of the invention that is administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth,

or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value of the compound at adenosine receptors.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in Tilburg *et al* (J. Med. Chem. (2002) 45, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of the invention that is administered may be an amount that results in a peak plasma concentration that is less than the lowest or highest Kd value of the compound at adenosine receptors (i.e. less than the lowest or highest Kd value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest Kd value.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest Kd value of the compound at adenosine receptors.

The K_d value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the K_d of the compound at each receptor.

Alternatively, the amount of a compound of the invention that is administered may be an amount that is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to the side effects.

Alternatively, the amount of a compound of the invention that is administered may be an amount that gives rise to plasma concentrations that are one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to

be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that causes the side effects.

It is expected that the amount of a compound of the invention that is administered should be 0.001-15 mg/kg. The amount may be less than 6 mg/kg. The amount may be at least 0.001, 0.01, or 0.1 mg/kg. The amount may be less than 0.1, or 0.01 mg/kg. Preferred ranges are 0.001-10, 0.001-5, 0.001-2, 0.001-1, 0.001-0.1, 0.001-0.01, 0.01-10, 0.01-5, 0.01-2, 0.01-1, 0.1-10, 0.1-5, 0.1-2, 0.1-1, 0.2-1.2, 0.2-1, mg/kg.

Preferred doses for a 70kg human subject are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7-70mg, or 14-70mg.

It is believed that the dosage amounts specified above are significantly lower (up to approximately 1000 times lower) than would be expected to be required for an anti-inflammatory effect based on the EC50 value of the compound at the adenosine A2A receptor.

The appropriate dosage of a compound of the invention will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

Compounds of the invention may be administered with or without other therapeutic agents, for example analgesics (such as opiates, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

In general, a compound of the invention may be administered by known means, in any suitable formulation, by any suitable route. A compound of the

invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular, subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

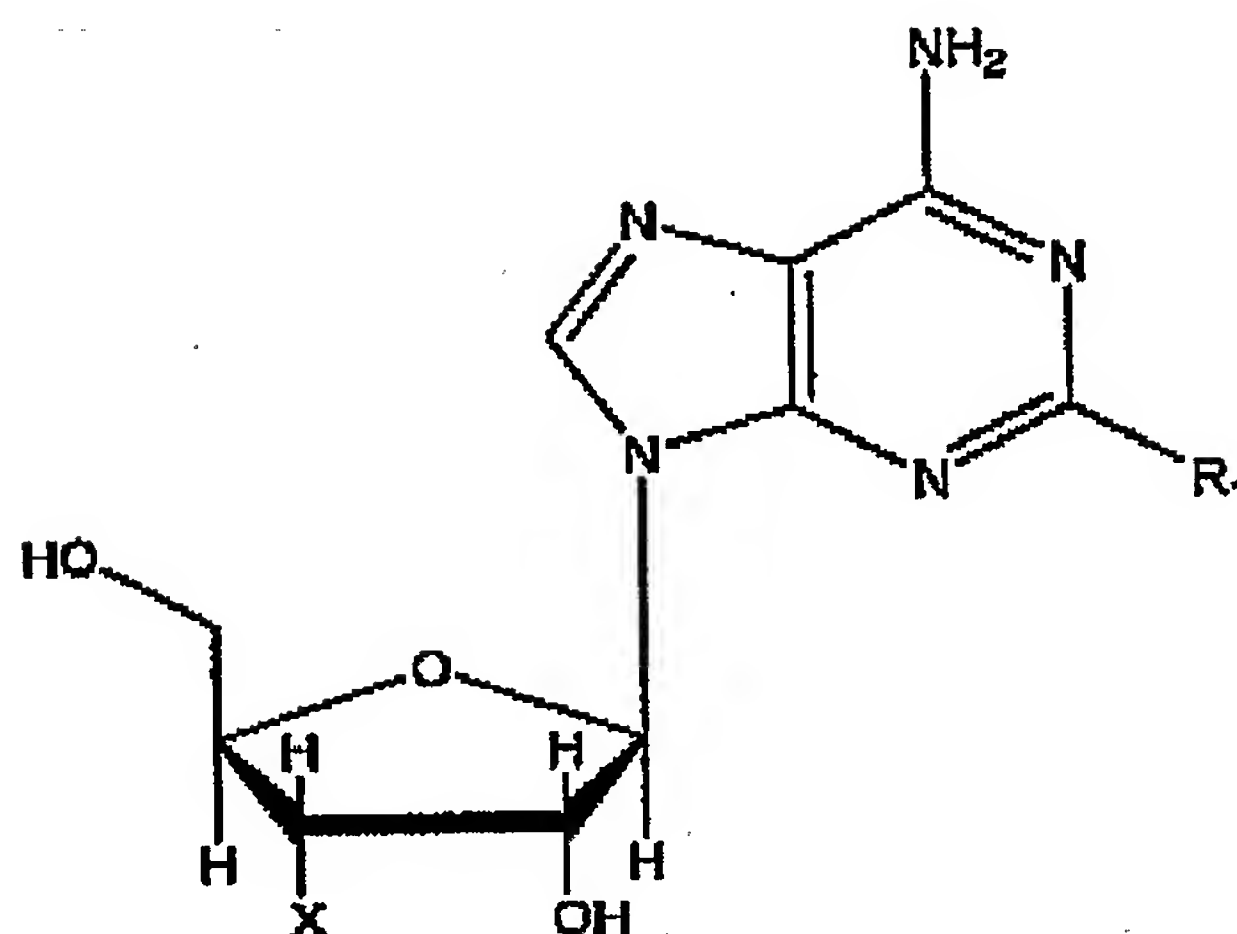
Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1-2mg, for example 0.5-1mg, typically about 0.2mg or 0.6mg of the active agent per kg of the (human) subject. At these levels it is believed that effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

A preferred administration frequency of a compound of the invention is expected to be two or three times per day.

Compounds of the invention can also serve as a basis for identifying more effective drugs, or drugs that have further reduced side effects.

Structures of preferred compounds of the invention are given in the Examples below. A K_i value is given for each compound. To calculate this, rat striatal membranes were incubated for 90 minutes at 22°C in the presence of 2nM [3H]-CGS21680, 1Unit/ml adenosine deaminase and increasing concentrations of the compound being studied, prior to filtration and liquid scintillation counting.

Example 1**When X = OH**

Compound No.	Structure R ₁	(K _i) nM
1	OCH ₃	1300
2	OCH ₂ CH ₂ CH ₂ CH ₃	280
3	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	1500
4	OPh	2500
5	O-(4-cyano)Ph	1300
6	O-(3-Ph)Ph	620
7	5-indanyloxy	760
8	O-(3-CH(CH ₃) ₂)Ph	560
9	NH(CH ₃)	1356
10	NHCH ₂ CH ₃	1200
11	N(CH ₃) ₂	13350
12	NHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	290
13	NHPh	160
14	NH-(4-MeO)Ph	55

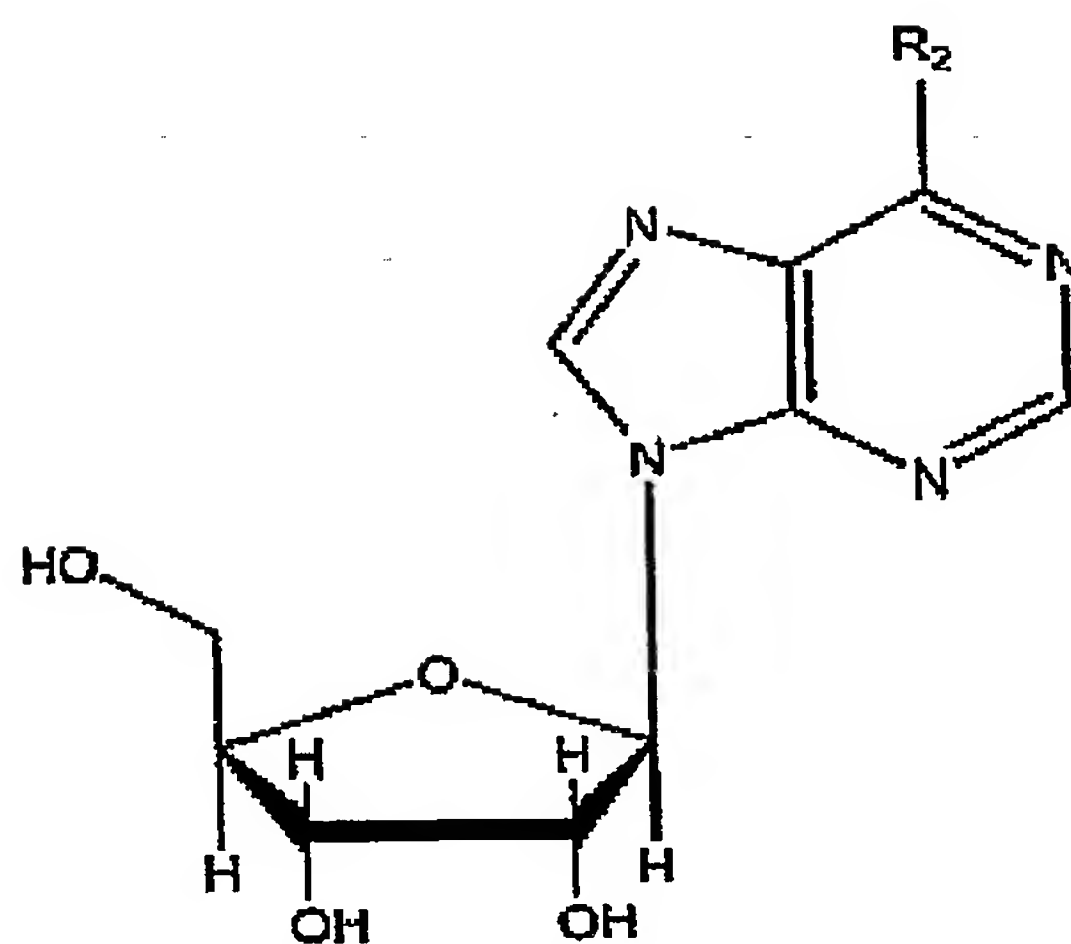


18	N-CH ₃ , N-CH ₂ CH ₂ CH(CH ₃) ₂	4000
19	OCH ₂ cyclopentyl	200
20	SO ₂ CH ₂ CH ₃	39000
21	OCH ₂ CH ₂ OH	203
22	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	800

When X = H

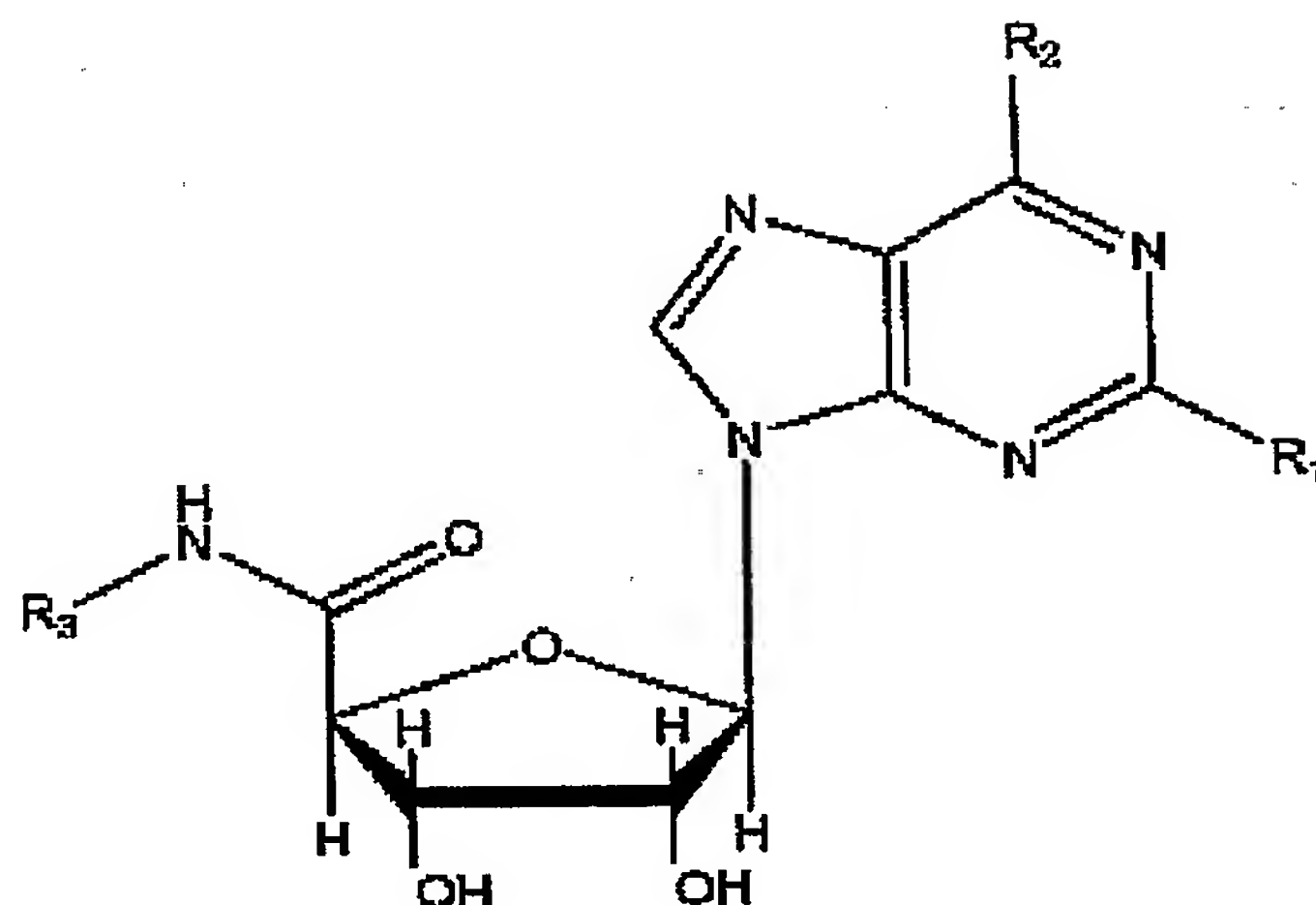
Compound No.	Structure R ₁	(K _i) nM
23	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	2990



Example 2

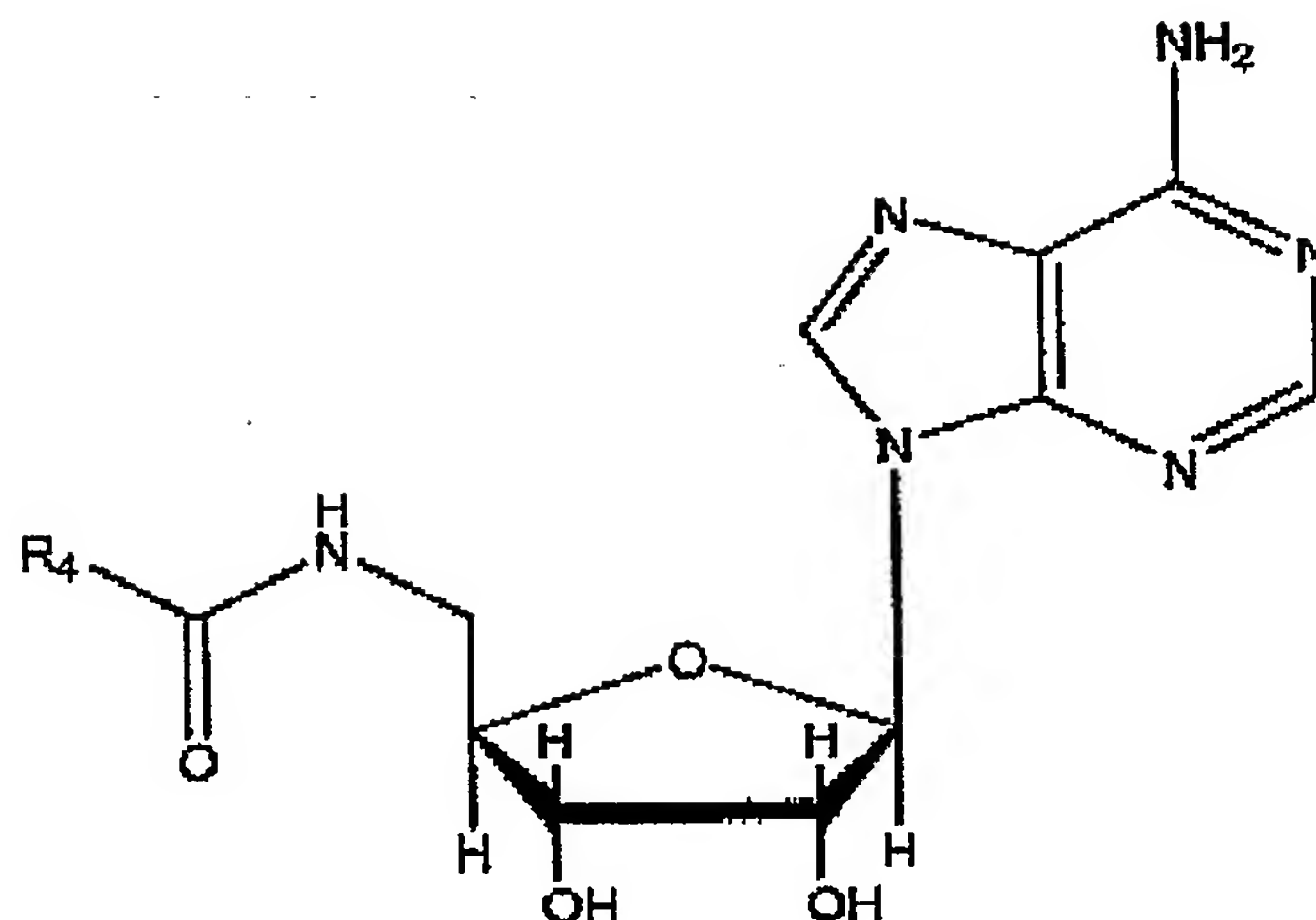
Compound No.	Structure R ₂	(K _i) nM
24	N(CH ₃) ₂	450000
25	NHCH ₂ CHC(CH ₃) ₂	8600
26	N-CH ₃ , N-CH ₂ Ph	18500
27	Piperaziny1	5000
28	N-Me, N-(CH ₂ CH ₂ OCH ₃)	13000



Example 3

Compound No.	R ₁	R ₂	R ₃	(K _i) nM
29	H	NH ₂	CH(CH ₃) ₂	1930
30	H	NH ₂	H	270
31	H	NHCH ₃	CH(CH ₃) ₂	2440
32	OCH ₃	NH ₂	Ph	26100



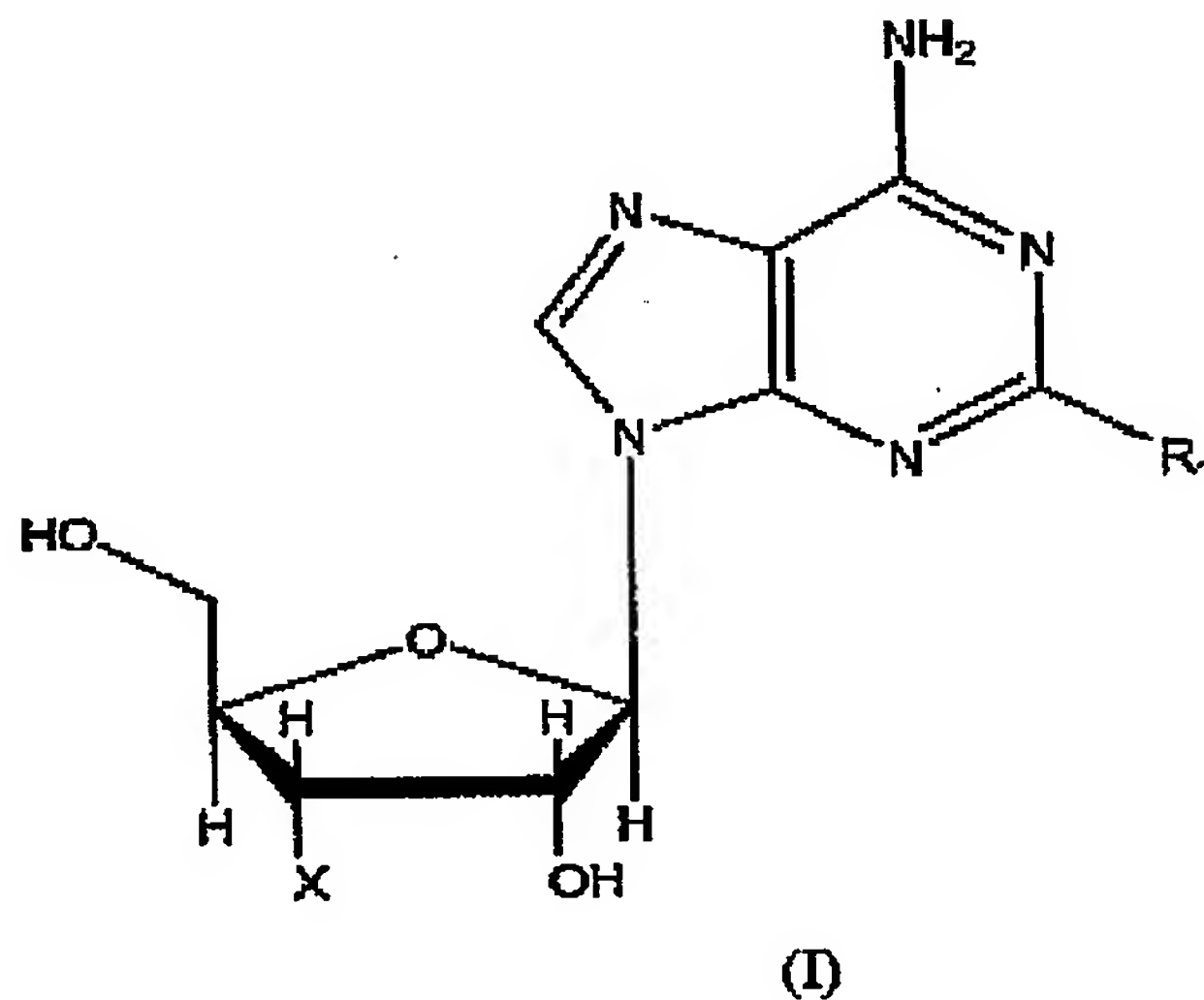
Example 4

Compound No.	Structure R_4	(KI) μM
33	$\text{CH}_2\text{CH}_2\text{CH}_3$	16900
34	NHCH_2CH_3	6570



Claims

1. A compound of formula (I), (II), (III), or (IV):

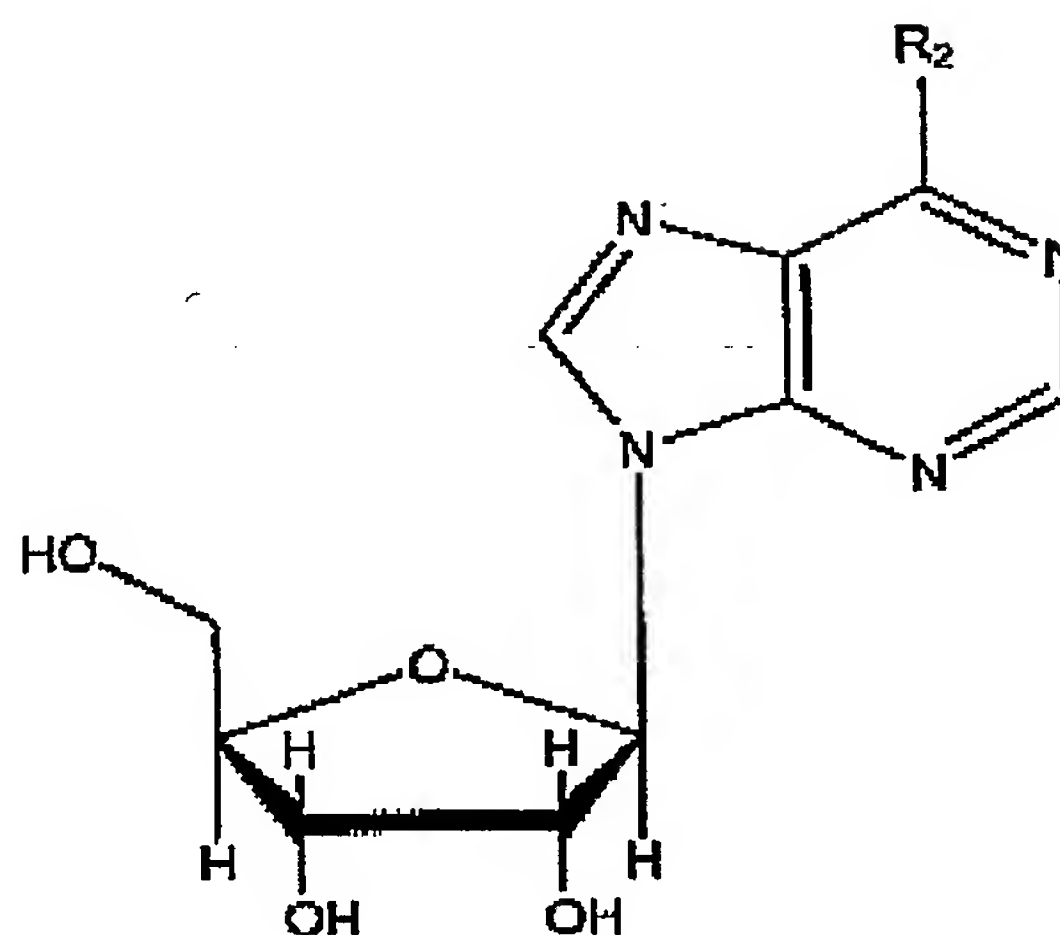


wherein:

when $X = OH$, R_1 is C_1 or C_4 - C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1 , C_2 , C_5 , or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH ; or

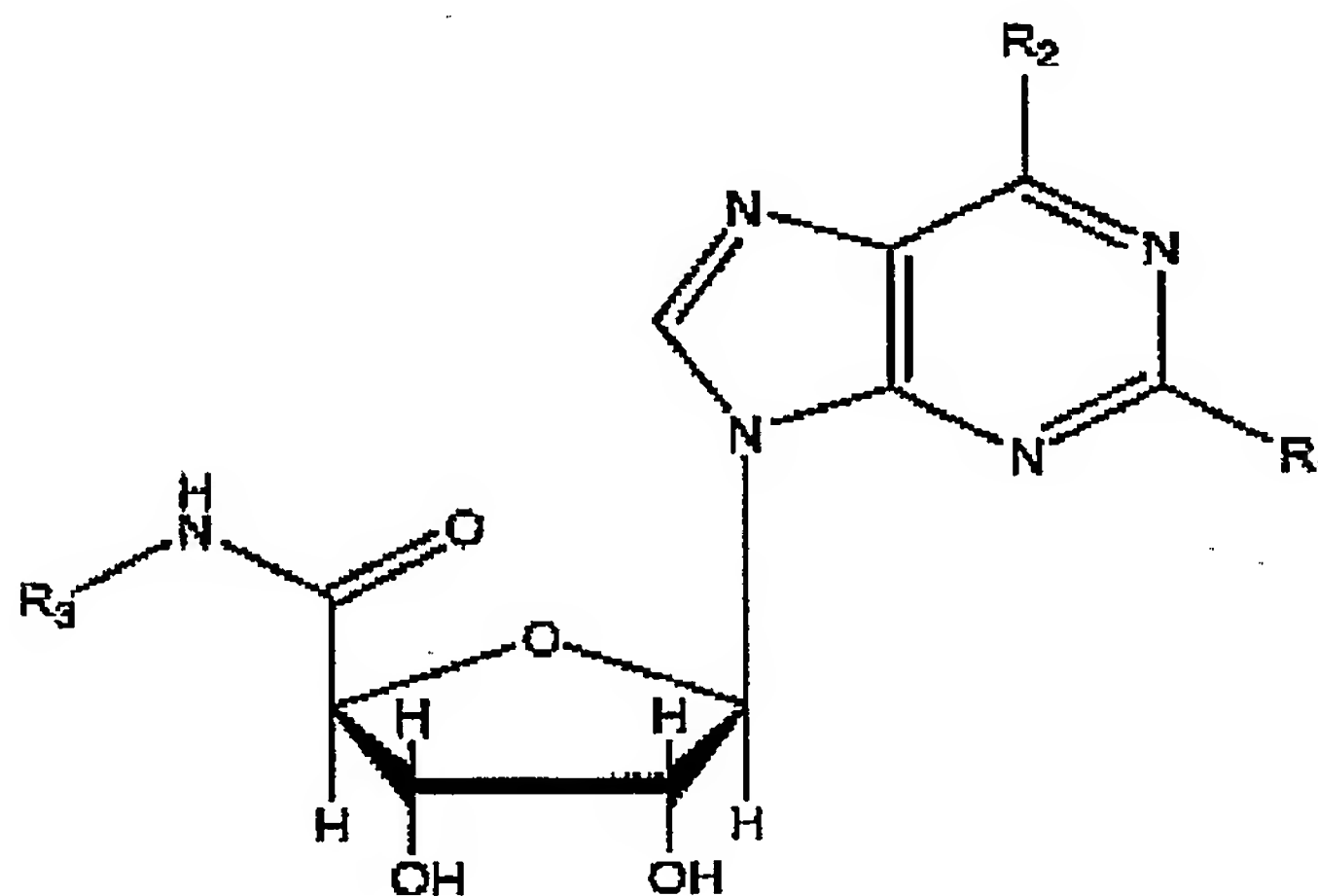
when $X = H$, R_1 is *n*-hexyloxy;





(II)

wherein R_2 is NMe_2 , N -(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



(III)

wherein:

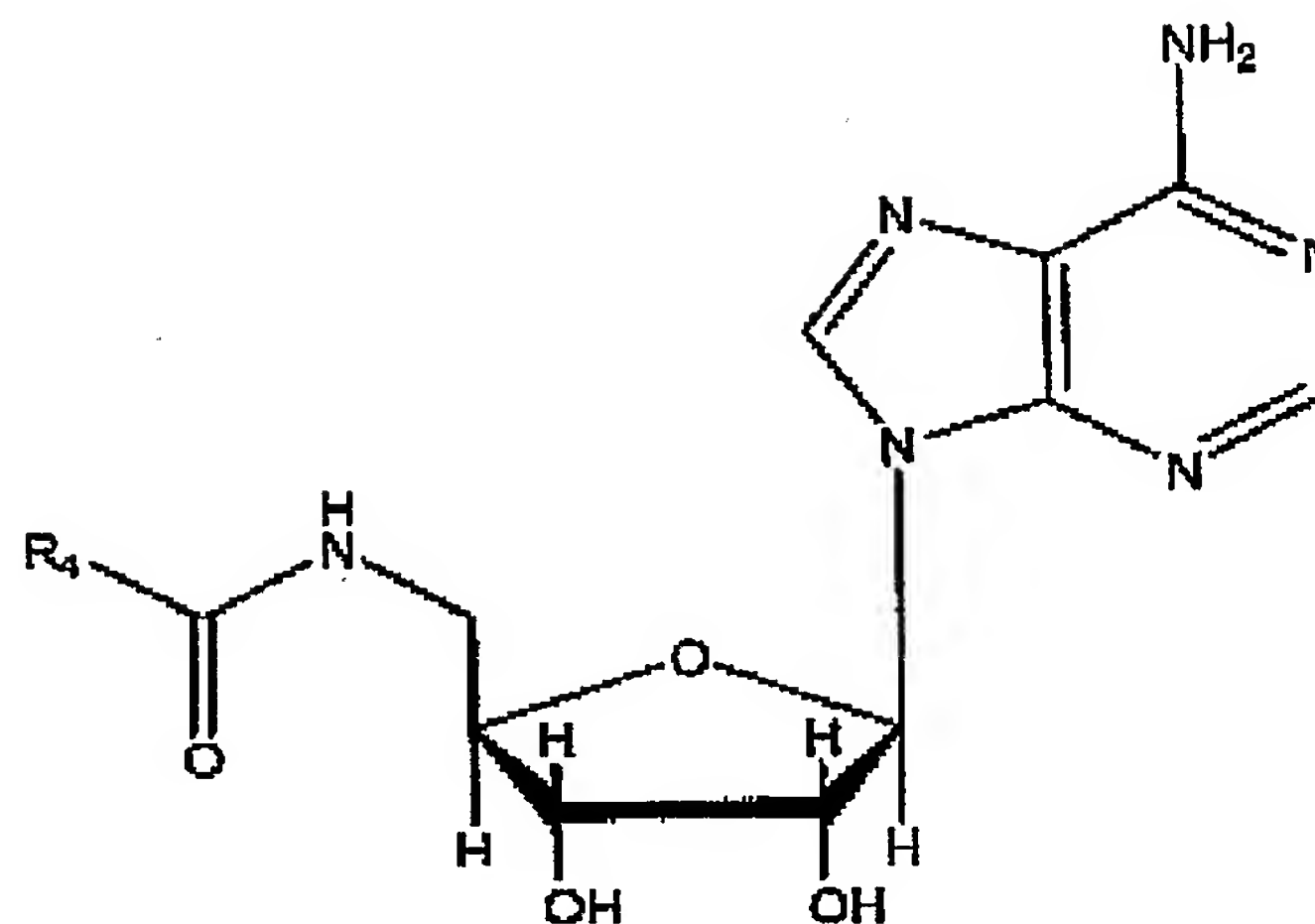
when $R_1 = H$, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group ($NHMe$); or

when $R_1 = H$, R_3 is H , and R_2 is NH_2 ; or

when R_1 is OMe , R_3 is Ph , and R_2 is NH_2 ;



when R_1 is OMe, R_3 is Ph, and R_2 is NH_2 ;



(IV)

wherein R_4 is *n*-propyl or NHCH_2CH_3 ;

for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

2. Use according to claim 1 for the prevention, treatment, or amelioration of inflammation caused by or associated with cancer, auto-immune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration, muscle fatigue or muscle cramp, arthritis, psoriasis, asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, organ transplant rejection, cachexia secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to

acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria, bacterial meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment.

3. A method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound as defined in claim 1 to a subject in need of such prevention, treatment, or amelioration.

4. A method according to claim 3 for the prevention, treatment, or amelioration of inflammation caused by or associated with cancer, auto-immune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration, muscle fatigue or muscle cramp, arthritis, psoriasis, asthma, chronic obstructive pulmonary disease, fibrosis, multiple sclerosis, endotoxic shock, gram negative shock, toxic shock, hemorrhagic shock, adult respiratory distress syndrome, cerebral malaria, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, organ transplant rejection, cachexia secondary to cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria, bacterial meningitis, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment.

5. A method according to claim 3 or 4, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

6. A method according to any of claims 3 to 5, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.
7. A method according to any of claims 3 to 6, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.
8. A method according to any of claims 3 to 7, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.
9. A method according to any of claims 3 to 8, wherein the compound is administered to the subject in an amount that is one ten thousandth to one fifth of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.
10. A method according to any of claims 3 to 9, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the minimum plasma concentration of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

11. A method according to any of claims 3 to 10, wherein the compound is administered at a dosage of 0.001 to 6 mg/kg.

12. A pharmaceutical composition in unit dose form comprising up to 500mg of a compound as defined in claim 1, and a physiologically acceptable carrier, excipient, or diluent.